CERTIFICATE

This is to certify that the dissertation entitled **"DESIGN AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLET."** is a bonafide and genuine research work carried out at Department of Pharmaceutics, K.K. College of Pharmacy by **Ms**.**B.SWETHA** during the year 2011-2012 under the supervision of **Mrs. Preetha.P, M.Pharm., Assistant Professor,** Department of Pharmaceutics. This dissertation submitted in partial fulfilment of the requirements for the award of degree of Master of Pharmacy (Pharmaceutics), by The Tamilnadu Dr. M.G.R Medical University, Chennai-32.

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SWETHA.B

ABBREVIATIONS

mg-milligrram

cm- Centimeters

BD- Bulk Density

TD- Tapped Density

HR- Hausner's Ratio

Kg- Kilogram

^{o}C- Centigrade

%RH- Percentage Relative humidity

RPM- Revolutions Per minute

V_d- Volume of Distribution

Drug substances are most frequently administered as solid dosage formulations, mainly by the oral route. The drug substance's physicochemical characteristics, as well the excipients added to the formulations, all contribute to ensuring the desired therapeutic activity. Some of the solid dosage forms are tablets, capsules, pills, lozenges, cachets and powders. Tablets and capsules are the most frequently used solid dosage forms, have been in existence since the nineteenth century, and are unit dosage forms, comprising a mixture of ingredients presented in a single rigid entity, usually containing an accurate dose of a drug.

1. TABLETS: [1]

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

Advantages:

a. Easy to handle

b. Variety of manufacturing methods

c. Can be mass produced at low cost

d. Consistent quality and dosing precision

e. Can be self - administered

f. Enhanced mechanical, chemical, and microbiological stability compared to liquid dosage forms

g. Tamperproof

h. Lend themselves to adaptation for other profiles.

Disadvantages:

a. Difficulty of swallowing by children and ill patients.

b. Drugs that are liquid at room temperature cannot be formulated in tablet dosage form.

c. Drugs with poor wetting and slow dissolution properties are difficult to convert into tablets.

d. Bitter tasted drugs need special treatment like coating.

e. Drugs with high doses are difficult to formulate.

1.2 GENERAL PROPERTIES OF TABLETS:

1. A tablet should have elegant product identity while free of defects like chips, Cracks, discoloration and contamination.

2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.

3. Should have the chemical and physical stability to maintain its physical attributes over time

4. The tablet must be able to release the medicinal agents in a predictable and reproducible manner.

5. Tablet must have a chemical stability to with stand in all the temperatures.

1.3 MODIFIED RELEASE DOSAGE FORM:[2]

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration.

1.4 TYPES OF DOSAGE FORMS:

1.4.1Oral Dosage Forms

Modified release dosage forms

Sustained release e.g. Controlled release

Prolonged release

Delayed release e.g. Enteric-coated tablets

1.4.2 Intramuscular Dosage Forms

Depot injections

Water-immiscible injections e.g. oils

1.4.3 Subcutaneous Dosage Forms

Implants

1.4.4 Transdermal Delivery Systems

Patches, creams, etc.

1.4.5 Targeted Delivery System

Sustained release drug delivery system is capable of achieving the benefit over the conventional dosage forms.

1.3 ADVANTAGES

1.3.1 Therapeutic advantages

Reduction in drug plasma level fluctuation; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

1.3.2 Reduction in adverse side effects

Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms

1.3.3 Patient comfort and compliance

Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

1.3.4 Reduction in healthcare cost

The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product. with reduction in side effects, the overall expense in disease management also reduced.

1.3.5 Avoid nights time dosing

It is also good for patients to avoid the dosing at night time**.**

1.4. DRAWBACKS ASSOCIATED WITH CONVENTIONAL DOSAGE FORMS:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.5 SUSTAINED DRUG DELIVERY SYSTEM:[3]

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects.

1.5.1 Drug Properties Relevant to Sustained – release Formulation:

The sustained-release products are often designed with an initial dose intended to establish rapidly therapeutic drug blood levels and additional drug intended to maintain those levels for prolonged periods. Those products providing only the slow-release component and lacking the immediate-release component have sometimes been termed prolonged release.

The term "sustained release" is used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

PROPERTIES AFFECTING PERFORMANCE OF SUSTAIN RELEASE FORMULATIONS:

A number of variables, such as drug properties including stability, solubility, partioning characteristics, protein binding, routes of drug delivery and the patient must establish the criteria for designing controlled/sustained release products. Physiochemical and biological factors since the biological properties of a drug are a function of its physiochemical properties while biological properties result from typical pharmacokinetic studies on the absorption, distribution, metabolism and excretion (ADME) characteristics of a drug as well as those resulting from pharmacological studies

A .Physicochemical Properties:

1. Aqueous solubility and P^{Ka}:

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility as shown by the Noyes – Whitney equation which, under sink condition, is

$$Dc/dt = KDACs$$

d_c/d_t= dissolution rate

KD = dissolution rate constant

A = total surface area of the drug particles and

Cs = aqueous saturation solubility of the drug

The dissolution rate is constant only if surface area, A, remains constant, but the important point to note is that initial rate is proportional directly to aqueous solubility Cs. Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Low solubility limits the dissolution rate and hence the absorption of many drugs.

In general, high aqueous solubility of a drug is undesirable for formulation into a sustained release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into a sustained released system is redundant.

2. Partition coefficient:

Partition coefficient is the measure of a drug‘s lipophilicity and an indication of its ability to cross call membrane

Between the time that a drug is administered and the time it is eliminated from the body, it must diffuse through a variety of biological membranes which act primarily as lipid-like barriers.

A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient, defined as

$$K = C_o/C_w$$

C_o = total concentration of all forms of the drug. E.g. ionized and unionized, in some organic phased at equilibrium, and

C_w = total concentration of all forms in an aqueous phase at equilibrium

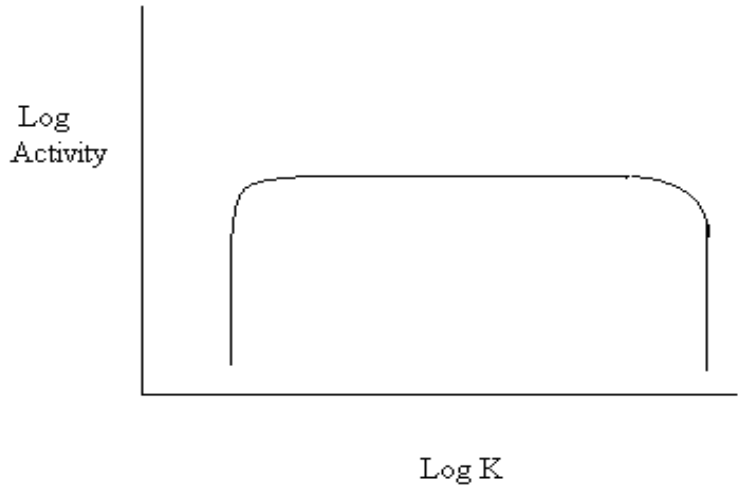


Figure: 1. Typical relationship between drug activity and partition coefficient K, Generally known as the Hansch correlation.

Drugs with a partition coefficient that either is extremely higher of lower that the optimum are, in general, poorer candidates for formulation into sustained release dosage forms.

3. Drug Stability:

The drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution; it would be seen possible to improve significantly the bioavailability of a drug, which is unstable in the GI tract by placing it in a slowly available sustained release form. For those drugs that are unstable in the stomach, the appropriate sustaining unit would be one that releases its contents only in the intestine.

Mostly sustained-release systems currently in use the release their contents over the entire length of the GI tract. Delivery systems that remains localized in a certain area of the GI tract and an act as reservoir for drug release are much advantageous for drug that not suffer from stability problems but have other bioavailability problems.

4. Protein Binding:

Distribution of the drug into the extra vascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for sustained drug release to extra vascular tissues, but only for those drugs that exhibit a high degree of binding.

Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug, and such drugs generally do not require a sustained-release dosage

form. However, drugs that exhibit a high degree of binding to plasma proteins also might bind to biopolymer in the GI tract, which could have an influence on sustained drug delivery.

The main forces of attraction responsible for bindings are Vanderwaals forces, hydrogen bonding and electrostatic forces. In general, charged compounds have a greater tendency to bind a protein than uncharged compounds, due to electrostatic effects. The presence of a hydrophobic moiety of the drug molecule also increases its binding potential. Some drugs that exhibit greater than 95% binding at therapeutic levels are Amitriptyline, Bischydroxycoumarin, Diazepam, Diazoxide, Dicumarol, and Novobioocin.

5. Molecular Size and Diffusivity:

In addition to diffusion through these biological membranes, drugs in many sustained-release systems must diffuse through a polymeric membrane or matrix that is used to control their release kinetics. The ability of a drug to diffuse through polymeric membrane or matrix that is used to control their release kinetics membranes is a function of its diffusivity (diffusion coefficient).

An important influence upon the value of the diffusivity, D, in polymers is the molecular size (or molecular weight) of the diffusing species. In most polymers, it is possible to relate log D empirically to some function of molecular size. Drugs with molecular weight up to 500-700daltons should presence no difficulty in its regard .Drugs with intermediate molecular weight of 50-400 daltons, diffusivities through a flexible polymer are typically of the $10^{-8}cm^2sec^{-1}$

$$\text{Log } D=-S_V \text{ LogV}+K_V=-S_M \text{ LogM}+K_M$$

Where,

D-diffusivity,

M-molecular weight

V-molecular volume

S_V, S_M, K_V, K_M=constant

B. Biological Properties:

1. Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a sustained-release system; since the rate limiting step in drug delivery from a sustained-release system is its release from the dosage form, rather than absorption, a rapid rate of absorption of the drug relative to its release is essential if the system is to be successful. The extent and uniformity of the absorption of a drug, as reflected by its bioavailability and the fraction of the total dose absorbed, may be quite low for a

variety of reasons. This usually is not a prohibitive factor in its formulation into a sustained-release system.

Some possible reasons for a low extent of absorption are poor water solubility, small coefficient, acid hydrolysis and metabolism, or site-specific absorption. The latter reason also is responsible for non-uniformity of absorption. Many of these problems can be overcome by an appropriately designed sustained-release system, as exemplified by the discussion under the potential advantages of sustained drug therapy.

2. Distribution:

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. This, in turn, influences the formulation of that drug into a sustained-release system, primarily by restricting the magnitude of the release rate and the dose size which can be employed. The apparent volume of distribution is merely proportionality constant which relates drug concentration in the blood or plasma to the total amount of drug in the body.

3. **Metabolism:**

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are Hydralazine, Salicylamide, Nitroglycerine, Isoproterenol, Chlorpromazine and Levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are Propoxyphene, Nortriptyline, Phenacetine, Propranolol and Lidocaine.

5. Elimination and Biological Half-life:

The rate of elimination of a drug is quantitatively described by its biological half-life, $t_{1/2}$. The half-life of a drug is related to large release rates and large doses. At the other extreme, a drug with a half-life of greater than 8 hours also probably should not be used; in most instances, formulation of such a drug into a sustained-release system its apparent volume of distribution V_d and its systemic clearance. A drug with a short half-life requires

frequent dosing and this makes it a desirable candidate for a sustained-release formulation.

In general, however a drug with a half-life if less than 2hours probably should not be used, since such systems will require unacceptably large release rates and large doses. At the other extreme a drug with a half-life of greater than 8 hours also probably should not be used in most instances, formulation of such a drug into a sustained-release system is unnecessary.

Some examples of drug with half-lives of less than 2 hours are Ampicillin, Cephalexin, Cloxacillin, Furosemide, Levodopa, Penicillin G and Propylthiouracil. Examples of those with half-lives of greater than 8 hours are Dicumarol, Diazepam, Digitoxin, Digoxin, Guanethidine, Phenytoin and Warfarin.

5. Side effects and Safety Considerations:

For some drugs, the incidence of side effects, in addition to toxicity, is believed to be related to their plasma concentration. As mentioned in the discussion on the potential advantages of sustained drug therapy, a sustained-release system can at times, minimize side over the time course of therapy.

The most widely used measure of the margin of safety of a drug is its therapeutic index, TI, defined in the following equation:

TI = TD50/ED50

TD50 is the median toxic dose and ED50 is the median effective dose. The value of TI varies from as little as unity, where the effective dose is also producing toxic symptoms, to several thousand. For very "potent" drugs, whose therapeutic concentration range is narrow, the value of TI is small. In general, the larger the value of TI, the safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into sustained-release products primarily due to technological limitations of precise control over release rates. Examples of drugs with values of TK10 are Aprobarbital, Digitoxin, Phenobarbital and Digoxin.

6. Dose size:

Sustained-release is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in the conventional dosage form will give some indication of the total amount needed in the sustained-release preparation. For those drugs requiring large conventional doses, the volume of the sustained dose may be as large as that to be impractical or unacceptable, depending on the route of administration. The same may be true of drugs, which require a large release rate from the sustained-release system, e.g. drugs with short half-lives.

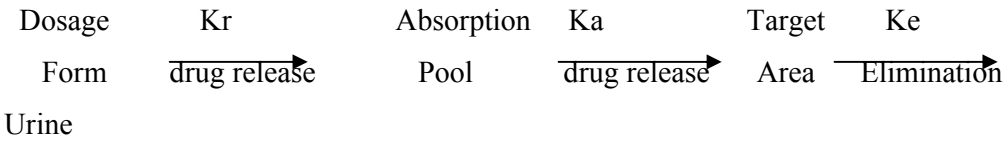
The mechanisms of release from these systems can be treated in two ways: (a) Extraction of the medicament by a simple diffusion process through enveloping homogeneous matrix, (b) Leaching of the medicament by the bathing fluid, which is able to enter the drug-matrix phase through pores, cracks and intergranular spaces.

When tablet ingredients are sensitive to moisture and are unable to withstand elevated temperature during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is known as dry granulation of pre-compression method or the double compression method.

A matrix is a uniform mixture of drug, excipients, (e.g.) polymer that is homogeneously fixed in a solid dosage form.

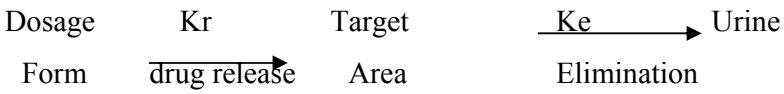
1.5.2 Basic kinetics of sustain drug delivery system:

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments and suppositories. For this discuss, these dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme:



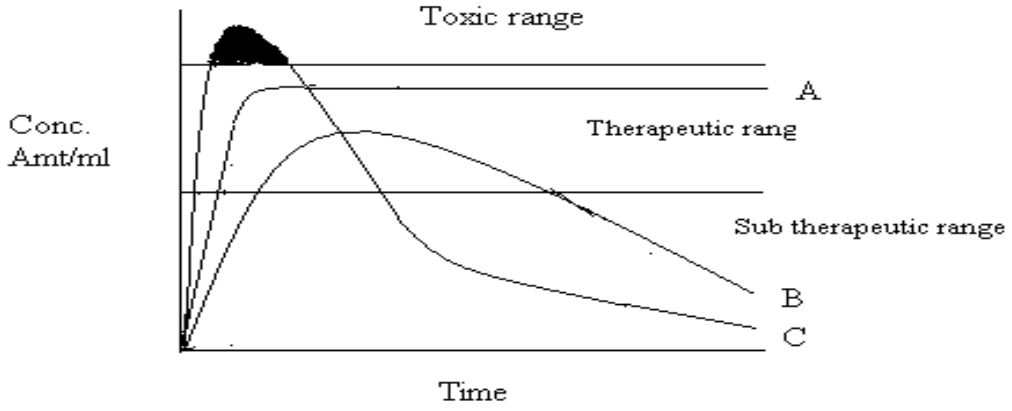
The absorption pool represents a solution of the drug at the site of absorption, and the terms Kr, Ka and Ke are first – order rate constants for drug release, absorption and overall elimination, respectively. Immediate release from a conventional dosage form implies that Kr>>>Ka or that observation of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in delivery of the drug to its target area.

For non immediate – release dosage form, Kr<<<Ka, that is, release of drug from the dosage form the rate-limiting step. This causes the above kinetic to reduce to the following:



Non-immediate-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release
    a. Controlled release
    b. Prolonged release
3. Site-specific release
4. Receptor release



A - Control Release Formulation

B - Sustain Release Formulation

C - Conventional Release formulation

Figure: 2. A Hypothetical plasma concentration-time profile from conventional Sustained and control delivery formula

1.5.3 Potential Advantages of Sustained Drug Therapy:

1. Avoid patient compliance problems.
2. Employ less total drug.
    a. Minimise or eliminate local side effects.
    b. Minimise or eliminate systemic side effects.
    c. Obtain less potentiating or reduction in drug activity with chronic use.
    d. Minimise drug accumulation with chronic dosing.
3. Improve efficiency in treatment
    a. Cure of control condition more promptly.

b. Improve control of condition, i.e. reduce fluctuation in drug level.

c. Improve bioavailability of some drugs.

d. Make use of special effects,

4. Economy

1.6. SELECTION OF DRUG FOR SUSTAINED RELEASE DRUG DELIVERY SYSTEM:

The choice of the drug substance is the most important decision in the successful development of a sustained-release product, Several categories of drug have potential for their therapeutics improvement of efficacy via sustained-release oral routes e.g. .Antianginal, Anti-inflammatory, Antihistaminic, Ant gastric resistant agents, Antipsychotic agents and Anti diabetic drugs of agents.

The common goal for increased duration is twice a day, or when feasible, once a day. Several properties of the drug itself can lead to the achievement of a 12 to 24 hours oral prolonged release dosage form. Some of the characteristics militating against success are the following:

1. Very short half-life and/or a relatively large single dose.
2. Long half-life.
3. Potent drug with a low margin safety.
4. Poorly soluble and/or poorly absorbed.
5. Biological activity not a function of core in blend.
6. Absorption primarily active through a 'window'.
7. Large first-pass metabolism.

The selection of both the drug and retardant polymers along with the filler excipients will impact on the mechanism and rates of drug release from monolithic systems. Cellulose derivatives and acrylic resin polymers comprise the group of polymers that are presently available as aqueous coatings for pharmaceutical dosage forms.

1.7. MATRIX TABLETS: [4]

These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having

different solubility properties, the drug is dispersed in swell able hydrophilic substances, an insoluble matrix of rigid non swell able hydrophobic materials or plastic materials.

1.7.1. CLASSIFICATION OF MATRIX TABLETS

A. ON THE BASIS OF RETARD MATERIAL USED IN THE MATRIX TABLET CAN BE DIVIDED IN TO FIVE TYPES:

1. Hydrophobic Matrices (Plastic matrices):

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles.

Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acryl ate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices:

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swell able controlled release systems.

4. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups:

1. Cellulose derivatives:

Methyl cellulose 400 and 4000cps; hydroxy ethyl cellulose; hydroxy propyl cellulose (HPMC) 25,100,400 and 1500 cps; Sodium car boxy methyl cellulose.

2. Non cellulose or semi synthetic polymers:

Agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.

3. Polymers of acrylic acid:

Corbopol 934, the most used variety.

4. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolised or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

B. ON THE BASIS OF POROSITY OF MATRIX:

Matrix system can also be classified according to their porosity and consequently, macro porous; micro porous and non-porous systems can be identified:

1. Macro porous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.7.2. ADVANTAGES OF MATRIX TABLET:

1. Easy to manufacture
2. Versatile, effective and low cost
3. Can be made to release high molecular weight compounds.

1.7.3 DISADVANTAGES OF THE MATRIX SYSTEMS:

The remaining matrix must be removed after the drug has been released. The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.8. POLYMERS USED IN MATRIX TABLETS:

Hydro gels

Polyhydroxyethyle methylacrylate (PHEMA)

Cross-linked polyvinyl alcohol (PVA)

Cross-linked polyvinyl pyrrolidone (PVP)

Polyethylene oxide (PEO)

Polyacrylamide (PA)

Soluble polymers

Polyethylene glycol (PEG)

Polyvinyl alcohol (PVA)

Polyvinyl pyrrolidone (PVP)

Hydroxypropyl methyl cellulose (HPMC)

Biodegradable polymers

Polylactic acid (PLA)

Polyglycolic acid (PGA)

Polycaprolactone (PCL)

Polyanhydrides

Polyorthoesters

Nonbiodegradable polymers

Polyethylene vinyl acetate (PVA)

Polydimethyl siloxane (PDS)

Polyether urethane (PEU)

Polyvinyl chloride (PVC)

Cellulose acetate (CA)

Ethyl cellulose (EC)

Hydroxy propyl methyl cellulose (HPMC)

Mucoadhesive polymers

Polycarbophil

Sodium carboxymethyl cellulose

Polyacrylic acid

Tragacanth

Methyl cellulose

Pectin

Sodium alginate

Natural gums

Xanthans gum

Guar gum

Karaya gum

1.9. DRUG RELEASE FROM MATRIX SYSTEMS:[5]

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

1.9.1 DERIVATION OF THE MATHEMATICAL MODEL TO DESCRIBE THIS SYSTEM INVOLVES THE FOLLOWING ASSUMPTIONS:

a) A pseudo-steady state is maintained during drug release;

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;

d) The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

$$dM/dh = C_o . dh - C_s/2 \text{ ----------} \square \ 1$$

Where

DM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to this theory

$$dM = (D_m . C_s / h).\ dt \text{ ----------} 2$$

Where:

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation 1 and equation 2 and integrating:

$$M=[Cs.Dm.(2Co-Cs).t]^{½} \text{----------} 3$$

When the amount of drug is in excess of the saturation concentration, then:

$$M = [2Cs.\ Dm\ .\ Co\ .\ t]^{½} \text{----------} 4$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [Ds.Ca.p/T.\ (2C_o - p.Ca)\ t]^{1/2} \text{----------} 5$$

Where:

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional pathlength

For pseudo steady state, the equation can be written as:

$$M= [2D.Ca.Co(p/T)t]^{1/2} \text{ ----------} 6$$

The total porosity of the matrix can be calculated with the following equation:

$$p=pa+Ca/\rho+Cex/\rho ex \text{ ----------} 7$$

Where:

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M=k.t^{1/2} \text{----------} \square 8$$

Where k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.

1.8.2 BIMODAL RELEASE:

In certain systems there is a bimodal or anomalous release of the active ingredient. In these systems there is diffusion; additionally, the extended release polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution.

A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodable matrix:

a) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix.

b) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.

c) Upon contact with water the drug dissolves and diffuses out of the device.

d) With increasing water content, the diffusion coefficient of the drug increase substantially.

e) In the case of a poorly water-soluble drug, dissolved and undissolved drug coexist within the polymer-matrix

f) Finally, the polymer self dissolves.

1.9.3 THESE SYSTEMS ARE DESCRIBED IN TERMS OF FRONTS. THE FOLLOWING FRONTS HAVE BEEN DEFINED, WITH REGARD TO ANOMALOUS RELEASE SYSTEMS:[6]

- The "**swelling front**", the erosion front, and the diffusion front. The swelling front separates the rubbery region (swelling polymer area) which has enough water absorbed

within the polymer to lower the Tg of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a Tg that is above the respective environmental temperature).

• The "**erosion front**" separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer concentration gradient and the well stirred medium.

• The "**diffusion front**" is between the swelling and erosion front and separated the areas of non dissolved drug from the area of dissolved drug.

With regard to swelling matrix systems, alternate models have been proposed to describe the diffusion, swelling, and dissolution processes occurring with into the system and these phenomena lead to drug release.

The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethylcellulose, hydroxypropylcellulose or tragacanth gums do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.

In 1985 Peppas introduced a semi-empirical equation describing the drug release behaviour from anomalous-release, hydrophilic matrix systems:

$$\mathbf{Q = k.\ t^{n}} \text{ ----------} \square 9$$

Where:

Q = Fraction of drug release in time (t)

t = Time

k = Rate constant (incorporates of polymer system and drug)

n = Diffusional exponent

The value of n is indicative of the drug release mechanism.

In order to describe relaxational transport, then modified equation 9 in order to account for relaxational transport:

$$\mathbf{Q = k_1 . t^{n} + k_2 . t^{2n}} \text{----------} \square 10$$

Where:

k1 =Fickain diffusion constant

k_2 = Relaxtional mechanism constant

If the surface area of the system is fixed, which is unlikely, the value of n should be 0.5 and equation 10 is transformed to:

$$Q = k_1 . t^{0.5} + k_2 . t \text{----------} \square 11$$

The first term of this equation accounts for diffusional phenomena, while the second term of this equation accounts for potote have been utilized in matrix type tablet formulations

1.10. EFFECT OF RELEASE LIMITING PARAMETER ON DRUG RELEASE:

The analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.[7]

A .Polymer hydration:

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The most important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B .Drug solubility:

Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C .Solution solubility:

In view of in vivo (biological) sink condition maintained actively by hemoperfusion; it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled slowly by the delivery system and is not affected or complicated by solubility factor.

D .Polymer diffusivity:

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion E_d has been acquired by the

diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer. The release of drug may be attributed to the three factors viz,

1) Polymer particle size

2) Polymer viscosity

3) Polymer concentration.

I. Polymer particle size:

Malamataris stated that when the content of hydroxypropyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxypropyl methylcellulose led to the burst release.

II. Polymer viscosity:

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

III. Polymer concentration:

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E. Thickness of polymer diffusional path:

The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

J_D=Ddc/dx

J_D flux of diffusion across a plane surface of unit area where D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

F .Thickness of hydrodynamic diffusion layer:

It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The

magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer $\delta_{d.}$

H .Drug loading dose:

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases.

In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position with in the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non dissolved and thus not available for diffusion. The solid drug remains with in tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

I .Surface area and volume:

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.

J. Diluent's effect:

The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

K. Additives:

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydro soluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

2. LITERATURE REVIEW:

1. K.SREENIVASA RAO et al 2011, studied development and evaluation of sustained release formulation of Venlafaxine hydrochloride by choosing it as a suitable candidate for sustain matrix tablet formulation. The drug was formulated into matrix tablet using hydrophilic polymer such as HPMC, Eudragit RS100 and ethyl cellulose as release retardants. Matrix tablet content a blend of HPMC and ethyl cellulose successfully sustained the release of Venlafaxine for a period of 17hrs.Venlafaxine F4 showed the sustained release of Venlafaxine as desired.[8]

2. KANIKA GOYAL et al 2009, studied formulation and evaluation of once-daily sustained release Venlafaxine hydrochloride tablet using hydrophilic matrix using hydrophilic gums and polymers such as Xanthan [Xgum], Guar gum [Ggum] and HPMC as a release modifier. The tablets are prepared by direct compression method. Xanthan gum along with HPMC K15M showed the sustained release of the drug for 20hrs.[9]

3. MC GOHEL et al 2009, studied modulation of Venlafaxine hydrochloride release from press coated matrix tablet by using HPMC K4M and HPMC K100M as release modifier in core and coat respectively. The kinetics of drug release was explained by Korsmeyer and Peppas model(anomalous non-Fickian diffusion).The systemic formulation approach enabled us to develop modified release Venlafaxine hydrochloride tablet.[10]

4. ASHWINI.R et al 2009. studied the design of sustained release matrix tablets of Venlafaxine hydrochloride using ion exchange resin with the incorporation of hydrophilic and hydrophobic polymer combinations. Validation of optimization study performed using five confirmatory runs, indicated very high degree of prognostic ability of response surface methodology .HPMC and ethyl cellulose can successfully employed as a once-a- day oral controlled release drug delivery system .[11]

5. ALTUL A.BODKHE et al 2008 designed extended release tablet of Venlafaxine hydrochloride using hydrophobic matrix. Matrix system based on non swell able was selected for sustaining the drug release. Different polymers and waxes viz. HPMC, stearic acid, acetyl

alcohol, ethyl cellulose etc. were used. Combinations of non swellable waxes with HPMC were also tried in order to get the desired sustained release profile over a period of 24hrs.[12]

6. SENTHILNATHAN et al 2011 developed Venlafaxine hydrochloride orodispersible tablet by using conventional technique such as superdisintegrant technology. Trails were conducted for the selection of superdisintegrant. In this sodium starch glycolate and crosscarmellose sodium are used in the rapid disintegration of tablets. The stability study was conducted for the optimized batch.[13]

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7. LADANI ANIKET et al 2011, studied fabrication of multi-layer matrix tablets of Venlafaxine hydrochloride using Hypromellose (HPMC K100M) and Xanthan gum. The tablets containing Venlafaxine hydrochloride 150mg were prepared using hybrid wet granulation barrier layer technology, using HPMC K100M as rate controlling ingredient in the middle layer and Xanthan gum in barrier layers. Drug release kinetic of the optimized triple layered tablets best fits to Higuchi model where as the release exponent value obtained for Korsmeyer Peppas model was less than 0.45, which is beyond the limit of the model. Release mechanism appears to be complex mechanism of swelling, diffusion, erosion and barrier controlled.[14]

8. BINDU MADHAVI B et al 2011, studied formulation and evaluation of Venlafaxine hydrochloride microspheres. The microspheres were prepared by emulsification and solvent evaporation method. The polymer used is ethyl cellulose. Drug polymer compatibility is done by FTIR studies. The method had resulted in good encapsulation efficiency and micron sized ethyl cellulose microspheres. The drug release was found to be sustained for 16hrs and follows Peppas kinetics.[15]

9. ZULKARNAIN KAMAL MOHAMMAD et al 2010 investigated the formulation and evaluation of mucoadhesive microspheres of Venlafaxine hydrochloride by using carbopol and HPMC K4M as mucoadhesive polymer. There was a sustained release up to 12hrs and almost 70% of mucoadhesion was observed after 12hrs.[16]

10. A.RAVINDRANATH et al 2010, studied formulation and evaluation of Venlafaxine hydrochloride enclosed in alginate micro beads prepared by Iontophoretic gelation method.

The micro beads were prepared by isotropic gelation of sodium alginate in calcium chloride solution. The method has resulted in good encapsulation efficiency and micron sized alginate spheres. The drug release was found to be sustained for 16hrs and follows Korsmeyer and Peppas kinetics.[17]

11. ADIMOOLAM SENTHIL et al 2011, investigated to formulate and evaluate the mucoadhesive Venlafaxine hydrochloride microspheres HPMC K4M as polymer. Microspheres were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross linking agent. The drug polymer compatibility studies were carried out by FTIR.As the concentration of glutaraldehyde increased the mucoadhesiveness decreases an there was no significant effect in time. Stirring speed has negative effect on t80.[18]

12. SOURABH JAIN et **al 2008**, studied preparation and evaluation of sustain release tablet of Furosemide using natural polymers such as Pectin, Guar gum and Xanthan gum .The tablet with guar gum have the greatest swelling index those than pectin and Xanthan gum. A better controlled drug release was obtained about (80.74%) approximately in15 hrs using this natural polymers.[19]

13.RAGHAVENDRA RAO.N et al 2009, studied the development of sustain release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz,HPMC and natural gums like karaya gum(KG) and carrageenan(CG). Among all the formulations, formulation F16 which contains 20% HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Tramadol hydrochloride was stable in the matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipient.[20]

14.V.MURUGANATHAN,SANDIP et al 2009,investigated the increase of therapeutic efficacyto reduce frequency of administration and improve patient compliance, by developing sustained release Zidovudine using different drug polymer ratio. Kollidon SR, Hydroxypropy l methylcellulose K15M, K100Mas matrix former.Among the different formulation B8 showe d sustained release of drug for 12 hours with 86.55% release. The regression coefficient

value of Higuchi plot was found to be 0.9925 that showed that drug was released by diffusion mechanism. The slope value of korsmeyer - peppas equation was found to be 0.5062 which indicating that drug was released by non-Fickain release mechanism.The R2 value indicates that drug release was limited by drug particle dissolution rate and erosion of thepolymer.Thus, drug in combination with Hydroxypropyl methylcellulose K100M were fou nd to be effective in retarding the release of Zidovudine.[21]

15. AFSAR C.SHAIKH et al 2009, studied to develop "once daily" sustained release tablets of Aceclofenac (200mg) by wet granulation using hydrophilic polymer like Hy droxy propyl methyl cellulose K -100M. FTIR studies shown there was no interaction betwee n drug and polymer. The drug release from optimized formulations was extended for a perio d of 4 hrs. The kinetic treatment of selected formulation (F8) showed that the release of drug follows zero order models. The optimized formulations were subjected to stability studies for one month at 45° temperature with RH 75±5% and showed there were no significant changes in drug content, physicochemical parameters and release pattern. Hydrophilic polymers in the preparation of matrix based sustained release formulation of Aceclofenac .[22]

16. SH LAKADE et al 2008, studied to develop hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. The influence of hydrophilic and hydrophobic polymer and granulation technique on Nicorandil was studied. The formulated tablet were also characterized by physical and chemical parameters, The in-vitro release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone. This formulation follows Peppas and Hixon crowel release kinetics.[23]

17. MD SHAID ALI et al 2010 studied to develop sustained release matrix tablets of Phenytoin sodium an antiepileptic drug. The tablets were fabricated by the wet granulation method using water as granulating agent along with matrix materials like guar gum, sodium alginate, tragacanth and xanthan gum with varying percentage. The I.R spectral analysis .studies confirmed no interaction between phenytoin with used natural gums. The formulation development process, F8 (55% guar gum with 10% acacia), the most successful formulation.

of the study, exhibited satisfactory drug release and could extend the release up to 12 hours. The mechanism of drug release from all the formulations was diffusion coupled witherosio.[24]

18. KALYANI CHITALURI et al 2011,sustaine release matrix tablets of Lostran potassium using Eudragit RLPO,RSPO and Ethyl cellulose individually and in combination. These matrix tablets were prepared by direct compression method. Drug-Excipient interaction was evaluated by differential scanning calorimetry and FTIR .The tablets prepared data shows individual concentration of RLPO,RSPO sustain the drug up to 10 hrs, with ethyl cellulose sustain the drug more than 12 hrs, Eudragit release the drug up to 12 hrs. The kinetics of drug release fallows Fickain diffusion mechanism.[25]

19. GANESH KUMAR et al 2010, studied Formulation and evaluation Monolithic matrix tablet of Acarbose using Hydroxypropyl methylcellulose and Eudragit in different concentration and combination, and sustained release behavior the fabricated tablets were investigated. Tablet prepared by direct compression method Standard curve and withdrawal samples were analyzed in UV-Vis spectrophotometery 625nm with alkaline potassium permanganate as coloring agent. formulations F1, F2, F3 wherein Hydroxypropyl methylcellulose K 100 M was employed, it was found that increasing the concentration of the polymer resulted in linearization of drug release curve and formulation F3 gave satisfactory drug release pattern. Formulations F4, F5, F6 containing Eudragit S-100 showed quite non-linearity in drug release. To analyze drug release mechanism Zero order, Higuchi model and Kosmeyer-peppas model were used.[26]

20. R MARGRET CHANDIRA et al 2010, studied to formulate and evaluate once daily extended release matrix tablets of Mirtazapine an atypical anti-depressant used in major depressive disorder. Alcoholic solution of povidone was used as granulating agent and hydrophilic matrix materials like Hydroxyl Propyl Methyl Cellulose, Poly Ethylene Oxide, and Carbopol were used as release controlling agents. The tablets were subjected to studies of thickness, hardness, weight variation, friability and in vitro release. According to theoretical release profile calculation, a once daily extend release formulation should release the 1.9 mg of Mirtazapine in 1 hour (6.88 % per hour). The results of dissolution studies indicated that formulation T-13 released the drug up to 14 hours in a zero order manner, and total release pattern was very close to the theoretical release profile.[27]

21. ROSHANPRADHAN et al 2010,a Hydroxypropyl methyl cellulose (HPMC K4M, HPMC K15M, and HPMC K100M) matrix tablet containing Indomethacin along with mannitol was formulated as a function of HPMC viscosity, and was compared with the commercial products.. The formulated products and two marketed products as reference sample were studied for its different physicochemical parameters and in vitro dissolution studies. It was found that the drug release profile decreases with increase in viscosity of polymer and, with increase polymer level in the formulations. Matrix tablets formulated employing drug: HPMCK15M: mannitol l: 1:0.25:1 and Drug: HPMC K15M: mannitol 1: 1:0.25:2 gave slow release of Indomethacin spread over 12 hours and their dissolution profiles were compared with the Indian marketed product.[28]

22. IZHAR AHMED SYED et al 2011, studied matrix and triple layer matrix tablets of metoprolol tartrate were formulated by using xanthan gum as the matrix forming agent and Sodium Carboxy Methyl Cellulose (Na CMC) as barrier layers. Mean dissolution time (MDT) for M3 and M3L3 were found to be 4.02h and 12.75h, while dissolution efficiency (DE8%) decreased, indicating that the release of metoprolol tartrate is slower from triple layer matrix tablets. The finding of the study indicated that the matrix tablets prolonged the release, but predominantly in a first order kinetics. Layering with Na CMC granules on the matrix core, provided linear drug release with zero order kinetics. FT-IR and DSC studies confirmed that there was no chemical interaction between drug and excipients used in the formulation.[29]

23. PADMASREE et al 2011, investigated effervescent floating matrix tablet of Famotidine are formulated to achieve gastric retention for a period 8-10 hrs. Natural polymers such as Xanthan gum and Chitosan were used to sustain release of the drug .Thus one tablet daily is sufficient to reduce gastric acidity as compared to conventional tablets of hyperacidity condition.[30]

24. CHADRAN. S et al 2008, studied Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. It was found that with increasing the proportion of ethyl cellulose in the matrix, the drug release was extended for 14-16 h. Incorporation of cellulose acetate phthalate in ethyl cellulose matrix provided very low initial release of the drug in the first 2-3 h followed by enhanced release rate in alkaline medium

owing to the high solubility of cellulose acetate phthalate at basic pH which led to creation of a porous matrix. It was found that with increasing the proportion of ethyl cellulose in the matrix for drug release was extended for 14-16 h. Incorporation of cellulose acetate phthalate in ethyl cellulose matrix provided very low initial release of the drug in the first 2-3 h followed by enhanced release rate in alkaline medium owing to the high solubility of cellulose acetate phthalate at basic pH which led to creation of a porous matrix.[31]

25. **A MESNUKUL et al 2009,** studied to fabricate the polyethylene glycol matrix tablet by mould technique. Indomethacin and HPMC were used as model drug and polymer in PEG matrix. The rate of drug release of tablet by using conventional technique such as superdisintegrant technology. Trails were conducted for the selection of superdisintegrant. In this sodium starch glycolate and crosscarmellose sodium are used in the rapid disintegration of tablets. The stability study was conducted for the optimized batch.[32]

3. AIM AND OBEJECTIVE:

Venlafaxine hydrochloride is an anti depressant drug

The main objectives of this study is to check the selected polymer's sustained drug delivery efficacy.

The primary goal of sustained drug delivery system is to reduce dosing frequency and enhance the drug absorption process in a specific manner in order to increase the half-life of the drug. The purpose of this research is to design and develop matrix tablet of Venlafaxine hydrochloride to sustain or control release of drug, which may reduce sudden peak levels of drug in blood

In summary, Venlafaxine hydrochlorides higher solubility in water results burst effect with sudden peak levels of drug in blood .By matrix formulation of the drug we can minimize the cost with patient compliance.

4. PLAN OF WORK:

1. Literature survey
2. Preformulation studies
3. Selection of Excipients
4. Formulation optimizations studies
5. In - vitro drug release studies
6. Statistical data analysis

STAGE 1:

Literature Review

Literature search is in done by various national and international journals.

STAGE 2:

Preformulation study

1. Development of calibration curve for Venlafaxine hydrochloride
2. Compatibility studies between drug & other additives
3. Drug excipient interaction study-FTIR

STAGE 3:

Formulation & evaluation of tablets

1. Preparation of Venlafaxine hydrochloride matrix tablet

2. To study the effect of certain process/formulation variables on the physicochemical and in vitro behaviour.

3. Evaluation of tablet for:

   a. Weight variation

   b. Hardness

   c. Friability

   d. Drug content assay

   f. In vitro Dissolution test

   e. Data model fitting

STAGE 4: Stability study.

5. DRUG PROFILE:

5.1 VENLAFAXINE HYDROCHLORIDE:

Synonyms: Effexor, Effexor XR

Chemical structure:

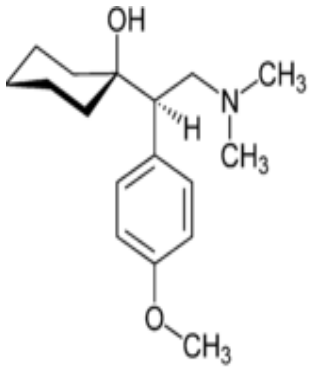


FIGURE NO :3 CHEMICAL STRUCTURE

The chemical structure of venlafaxine is designated (R/S)-1-[2-(dimethylamino)-1-(4 methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[a [a- (dimethylamino)methyl] p-methoxybenzyl] cyclohexanol hydrochloride

Empircal formula : C17H27NO2

Mol. Mass :277.402g/ml

Pharmacokinetic data

Bioavailability: 45%

Protein binding: 27%

Metabolism : hepatic

Half-life : 5±2h,

Excretion : renal

Physical/chemical properties:

Colour: It is a white to off-white crystalline powder.

Odour: no odour.

Taste: slightly bitter in taste

Solubility: It is freely soluble in and chloroform. In soluble in ether

Mechanism of action:

Venlafaxine is a bicyclic antidepressant, and is usually categorized as a serotonin-norepinephrine reuptake inhibitor (SNRI), but it has been referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor.[33,34] It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse. The neurotransmitters affected are serotonin (5-hydroxytryptamine) and norepinephrine (noradrenalin). Additionally, in high doses it weakly inhibits the reuptake of dopamine, with recent evidence showing that the norepinephrine transporter also transports some dopamine as well, implying that SNRIs may also increase dopamine transmission. This is because SNRIs work by inhibiting reuptake, i.e. preventing the serotonin and norepinephrine transporters from taking their respective neurotransmitters back to their storage vesicles for later use. If the norepinephrine transporter normally recycles some dopamine too, then SNRIs will also enhance dopaminergic transmission. However, while concurrent increase in dopamine (particularly in the prefrontal cortex) is likely to occur [50], the antidepressant effects of any drug are believed to result largely from the modulation of serotonin and norepinephrine; dopamine is thought to play a comparatively small role in depression.

Approved:

Venlafaxine is used primarily for the treatment of major depression, generalized anxiety disorder, social anxiety disorder, obsessive–compulsive disorder, panic disorder, and menopausal hot flashes in adults.

Depression:

Multiple double blind studies show venlafaxine's effectiveness in treating depression. Venlafaxine has similar efficacy to the tricyclic antidepressants amitriptyline (Elavil) and imipramine and is better tolerated than amitriptyline. Its efficacy is similar to or better than sertraline (Zoloft) and fluoxetine (Prozac), depending on the criteria and rating scales used. Higher doses of Venlafaxine are more effective, and more patients achieved remission or were "very much improved". The efficacy was similar if the number of patients who achieved "response" or were "improved" was considered. A meta-analysis comparing Venlafaxine and combined groups of SSRI or tricyclic antidepressants showed venlafaxine's superiority. Judged by the same criteria, Venlafaxine was similar in efficacy to the atypical

antidepressant bupropion (Wellbutrin); however, the remission rate was significantly lower for Venlafaxine In a double-blind study, patients who did not respond to an SSRI were switched to Venlafaxine or citaloprarm.

Drug interactions:

Venlafaxine should be taken with caution when using St John's wort Venlafaxine may lower the seizure threshold, and co-administration with other drugs that lower the seizure threshold such as bupropion and tramadol should be done with caution and at low doses .[35] There have been false positive phencyclidine (PCP) results caused by Venlafaxine with certain on-site routine urine-based drug tests. Although the synergistic effects may not be as bad as with other anti-depressants, it is still not recommended to take Venlafaxine with alcohol.

Common side effects:

Headache (34%)
Nausea (21-35%)
Insomnia (15-23%)
Sexual dysfunction (14-34%)
Dry mouth (12-16%)
Dizziness (11-20%)
Sweating (10-14%)
Decreased Appetite (8-20%)
Abnormal ejaculation (8-16%)
Hypertension (4-5%)
Vivid/Abnormal dreams (3-7%)
Akathisia (Agitation) (3-4%)
Decreased libido (3-9%)
Increased yawning (3-5%)
Apathy
Constipation
Increased anxiety at the start of treatment
Drowsiness

Increased anxiety at the start of treatment

Drowsiness

Dose dependency of adverse events:

A comparison of adverse event rates in a fixed-dose study comparing Venlafaxine 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with venlafaxine use. The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the Venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one Venlafaxine group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value <=0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

Memory loss:

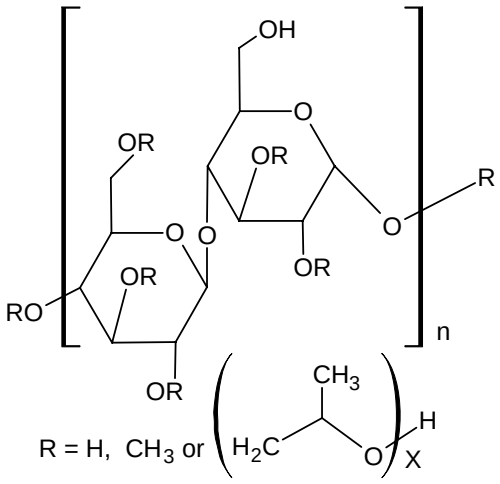
In a study of 70 patients that compared the tolerability of Venlafaxine at standard doses, ranging from 75 to 300 mg, against relatively high doses (rarely prescribed), ranging from 375 to 600 mg per day, for treating DSM-IV major depressive disorder "failing memory" was reported in 44% of cases. The severity of Venlafaxine-induced memory loss was also noted to increase with dose and length of treatment.

Over dosage:

Overdosing with the drug can result in cardiac arrhythmia, hypotension, seizures, coma or even death. Plasma Venlafaxine concentrations in overdose survivors have ranged from 6-24 mg/l, while post-mortem blood levels in fatalities are often in the 10-90 mg/l range.

6. EXICIPIENT PROFILE:[36]

6.1 HYDROXY PROPYL METHYL CELLULOSE



It is mixed alkyl hydroxyl cellulose ether and may be regarded as the propylene glycol of methyl cellulose .

Non-proprietary Name:

USP : Hydroxylpropyl methyl cellulose 2208, 2906, 2910.

BPC : Hypromellose

Serviceable Categories:

USP:Suspending and viscosity-increasing agent, tablet binder coating agent.

BP :Viscosity increasing agent; adhesive anhydrous ointment ingredient.

Other : Film former, emulsion stabilizer.

Chemical name : Cellulose - 2-hydroxy propyl methyl ether.

Empirical formula :$C_8H_{15}O_6$-($C_{10}H_{18}O$)n- $C_8H_{15}O_5$.

Grades: Methocel - E5, E15, E4M, R50, F4M, K100, K4M, K15M, K100M.

Descrription : An odorless, tasteless, white or creamy white fibrous or granular powder.

Molecular weight : Approximately 80,000.

Density : 0.25 – 0.70g/cm^3

Viscosity : HPMC-E15, 15 cps (2% aqueous solution),
HPMC-E4M, 4000 cps (2% aqueous solution)
HPMC-K4M, 4000 cps (2% aqueous solution)

P^H : 6.0 – 8.0 (1% aqueous solution)

Typical Properties:

Specific gravity : Approximately 1.3

Apparent density : $0.25 – 0.70 g/cm^3$

Browning temperature : $190 – 200^0C$ ($374-392^0F$)

Charring temperature : $225 – 230^0C$ ($437 – 446^0F$)

Enzyme resistance : Comparatively enzyme-resistance providing excellent viscosity stability during long term storage.

Solubility:

Soluble in cold water, forming a viscous colloidal solution. Insoluble in ether, alcohol and chloroform. But soluble in mixtures of methanol and methylene chloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents.

Stability: Very stable in dry conditions

Safety: Hydroxy propyl methylcellulose has been shown to be safe in humans and in animals.

Incompatibility: It is in compatible at extreme pH conditions and in the presence of oxidizing materials

Applications in pharmaceutical formulations

It is used as a film former, lower viscosity grades are used in aqueous film coating and higher viscosity grades are used in solvent film coating.[37] The concentration varies from 2 to 10% depending upon viscosity grade of the polymer. It is also used as tablet binder. The E grades are generally suitable as film former while the K grades are used as thickeners.

6.2 SODIUM ALGINATE [38]

Nonproprietary Names

BP :Sodium Alginate

PhEur :Sodium Alginate

USP-NF :Sodium Alginate

Synonyms

Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol;Keltone; natrii alginas; Protanal; sodium polymannuronate.

Chemical Name and CAS Registry Number:

Sodium alginate [9005-38-3]

Empirical Formula :

Sodium alginate consists chiefly of the sodium salt of alginic acid,which is a mixture of polyuronic acids composed of residues of Dmannuronic acid and L-guluronic acid.

Functional Category:

Stabilizing agent;

Suspending agent;

Tablet and capsule disintegrant;

Tablet binder;

Viscosity increasing agent.of sodium chloride is present.

Applications in Pharmaceutical Formulation :[39,40]

1 Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.

2 In tablet formulations, sodium alginate may be used as both a binder and disintegrant;

3 It has been used as a diluent in capsule formulations

4 Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets,

5 Aqueous suspensions.

6 The effects of particle size, viscosity and chemical composition of sodium alginate on drug release from matrix tablets have been described.

Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Uses of sodium alginate.

Pastes and creams	5–10
Stabilizer in emulsions	1–3
Suspending agent	1–5
Tablet binder	1–3
Tablet disintegrant	2.5–10

Pharmacopeial Specifications

Microbial limits	- 41000 cfu/g 4200 cfu/g
Loss on drying	- 415.0% 415.0%
Ash	- 18.0–27.0%
Sulfated ash	- 30.0–36.0%
Arsenic	- 41.5 ppm
Calcium	-41.5%
Chlorides	-41.0%
Lead	- 40.001%
Heavy metals	-420 ppm 40.004%
Assay (dried basis)	-90.8–106.0%

Stability and Storage Conditions

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidifies and a cool temperature. Aqueous solutions of sodium alginate are most stable at pH4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years.(39)Solutions should not be stored in metal containers. Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Solutions are ideally

Incompatibilities

Sodium alginate is incompatible with acridness derivatives, crystal violet, phenyl mercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4%.

6.3. AVICEL P^H101: [41]

Synonyms

Micro crystalline cellulose.

Alternate product name:

Avicel P^H 102,103,105,112,113,200,301,302,200LM.

Physical and Chemical properties:

Odour- ordourless

Appearance- white, free flowing powder

P^H – (In solution) 5.0-7.0 (11% solid dispersion)

Specific gravity- (H_20=1) Bulk density,0.2-0.5/cc

Incompatibilities:

Incompatible with strong oxidizing agents

Applications:

-Roller compaction

-Wet granulation

- Direct compression

-Extrusion/spheroiozation

6.4. MAGNESIUM STEARATE:[42]

Synonyms:

Dibasic magnesium stearate; Magnesium distearate; Magnesium octadexonate; Octa deconic acid; Magnesium salt; stearic acid

Empirical Formula:

$C_3H_6O_7MgO_4$

Functional Category:

Tablet and capsule as lubricant.

Description:

Magnesium stearate is a very fine powder, white precipitated milled, having a faint odour of stearic acid.

Solubility:

Insoluble in ethanol, ethanol (95%), ether& water; slightly soluble in warm benzene & warm ethanol.

Stability & storage:

Magnesium stearate is stable; it is closed in a container stored in cool dry place.

Incompatibilities:

Incompatible with strong acids, alkali and iron salts. Avoid mixing with strong oxidized materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins & most alkaloid salts.

Applications:

Magnesium stearate is widely used in cosmetics, food& and pharmaceutical formulations. It is primary used as lubricant in capsule and tablet manufacturing at concentrations between 0.25% and 5.0% w/w **.**It is also used in barrier cream.

2.6. TALC:[43]

Synonyms:

Kerolite

Magnesium talc

Soap stone

Steatite-Massive

Chemical formula:

$Mg_3 Si_4O_{10}(0H)_2$

Molecular weight:

379.27

Density:

2.7-2.8

Solubility:

Not soluble in water, slightly soluble in dilute mineral acids

Stability:

Stable

Storage:

Stored in air tight container

Applications:

Talc widely used in oral dosage formulation as a lubricant and diluents. It is widely used as dissolution retardant in the development of controlled release products. Talc is also used as a lubricant in tablet formulations, in a novel powder coating for extended release pellets and as an adsorbent.

7. MATERIALS AND EQUIPMENTS:

7.1 MATERIALS:

S.N0	MATERAILS	COMPANY
1	Venlafaxine hydrochloride	Celon laboratories, Hyderabad.
2	Hpmc K15M	Sigma chemical limited, Bangalore.
3	Sodium alginate	SD fine chemical limited, Mumbai.
4	Avicel P^{H}101	Sigma chemical limited, Bangalore.
5	Magnesium stearate	SD fine chemical limited, Mumbai.
6	Talc	SD fine chemical limited, Mumbai.

7.2 EQUIPMENTS:

S.NO	EQUIPMENT	MANUFACTURE	MODEL NO
1	Electronic semi micro balance	Sartorius	ME 2350
2	Mesh	Retsec	-
3	Tapped density tester	Electro lab	ETD-2
4	Electromagnetic sieve shaker	Electro pharma	EMS-8
5	Rapid mixer granulator	Diosna	ESS355-002
6	Retch drier	Retch	TG200
7	Compression machine(single rotatory)	Cad match	CMD3-16
8	Dissolution test apparatus	Electro lab	ED-22
9	Hardness tester	Dr Scheleuniger pharmatron	8M
10	Moisture balance	Sartorius	MA-I50
11	Friabilator	Electro lab	EF-100
12	Induction sealer	Sigma jr electronic devices	Csp-200
13	Stability chambers	Thermo lab	-
14	IR Spectrophotometer	Perkin Elmer	1600

8. EXPERIMENTAL SECTION:

8.1 PREFORMULATION STUDIES:

Preformulation testing is an investigation of physical and chemical properties of drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms. The scope of Preformulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product.

In the present study, therefore, calibration of Venlafaxine hydrochloride, compatibility with the selected polymers using FTIR peak matching, etc

8.2. DEVELOPMENT OF CALIBRATION CURVE FOR VENLAFAXINE HYDROCHLORIDE:

As have Venlafaxine hydrochloride high solubility, so the calibration curve was obtained by using distilled water.

A stock solution of Venlafaxine hydrochloride was prepared by dissolving 100 mg of the drug in 100 ml of distilled water to get 1 mg/ml solution(stock solution). From this 10 ml of solution was pipette out and diluted to 100 ml using distilled water to produce 100 µg/ ml, from this 0.5ml of solution was diluted to 10 ml using water to get 5 µg/ ml. from this working stock solution, dilution were made with distilled water to produce 10, 15, 20, and 25 µg/ ml. The λmax of the drug was determined by scanning one of the middle concentration between 200 nm to 400nm using a cyber lab uv 100 double spectrophotometer. At this wavelength, the absorbance's of all the dilutions were measured against the blank. Standard curve between concentration and absorbance was plotted and slope (K) and intercept (B) values were determine.

7.3 COMPATIBILITY STUDIES:

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm-1 in a

Shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peak.

8.4 FORMULATION DEVELOPMENT:

Matrix tablets of Venlafaxine hydrochloride were formulated by using HPMC K15M and sodium alginate as a polymers and were prepared by wet granulation technique.

In the formulation of matrix tablets, Venlafaxine hydrochloride was used as model drug, selected HPMC K15M and sodium alginate were used as polymer, Microcrystalline cellulose (Avicel pH 101) was used as diluents, Talc and Magnesium stearate used as lubricant and glidant.

8.5 PREPARATION OF GRANULES AND COMPRESSION OF TABLETS :[44]

The granules were prepared by wet granulation technique and water was used as granulating agent. Accurately weighed quantities of the ingredients were pass through sieve no 16 and mixed with planetary mixer required quantity of water was added and mixed thoroughly until get suitable granules. The granules were passing through British Standard Sieve (BSS) No.16. Wet granules were dried in hot air oven for at 60oc till to get the moisture content approximately 3% and again passed through BBS No. 22 mesh granules were placed on the rotating hydraulic 8 station compression machine and compressed into tablets of 200mg each tablet with the following qualities

1. Tablet weight
2. Diameter
3. Thickness
4. Hardness

8.6 THE GENERAL FORMULA IS GIVEN IN THE BELOW TABLE:

TABLE NO: 3 General formula

S.No.	Name of the ingredient	Quantity per tablet (mg)	Uses
1	Venlafaxine hydrochloride	100mg	Drug
2	Hpmc k15M	25 to75mg	Polymer
3	Sodium alginate	2 to 3mg	Polymer
4	Avicel pH 101	18 to 70mg	Diluents
6	Magnesium stearate	2mg	Lubricant
7	Talc	2mg	Glidant
8	Water	q.s	Granulating agent

8.7 FORMULATION OF DIFFERENT BATCHES IS GIVEN IN THE TABLET:

Table no: 4 Formulation for different batches

INGREDIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Venlafaxine hydrochloride	100	100	100	100	100	100	100	100	100
Hpmc k15M	25	75	50	75	75	45	25	40	25
Sodium alginate	2	3	3	2	2.5	2.5	2	2.5	3
Avicel pH 101	68.5	18	43	19	18.5	43.5	69	44	68
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	200	200	200	200	200	200	200	200	200

8.8 PRECOMPRESSION EVALUATION OF GRANULES:

8.8.1 Angle of Repose:

The angle of repose of the prepared pellets was measured by funnel method. A dry clean funnel was kept on a burette stand at particular height (2-3cm). A graph paper was placed on the flat surface and a sufficient quantity of the spheroids was allowed to flow slowly through the funnel until the heap touched the tip of the funnel. The circumference of the heap was drawn and the midpoint was located and its radius was measured. The angle of repose was calculated by:

Tan θ = h/r or θ =tan-1h/r.

Where, h = height of pile;

r = radius of the base of the pile and

θ = angle of repose.

8.8.2 Bulk density:

The bulk density of the prepared granules was measured by automated tape. A weighed amount of granules was introduced into a graduated measuring cylinder. The cylinder was fixed on the bulk density apparatus and the timer knob was set for hundred tapping. After tapping the volume occupied by the granules was noted as final volume. Then the bulk density was calculated using:

Bulk density = Wt. of sample (g) / Final volume (cc)

8.8.3 Measures of Powder Compressibility:

The Carr's Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Carr's Index and the Hausner Ratio, which are calculated using the following formula:

Carr's Index = (Vr-Vo) X 100 / Vr

Where,

Vr = Tapped density

Vo = Bulk density

8.8.4 True density:

The true density of the prepared granules was determined by liquid displacement method.

Select a solvent in which the granules are insoluble and heavy.

Method: Pycnometer or specific gravity bottles may be used.

Weight of Pycnometer = W1

Weight of Pycnometer + sample = W2

Weight of sample = W3 = W2 - W1

Weight of Pycnometer with sample and filled with solvent = W4

Weight of liquid displaced by solid = W4 - W2

$$\text{True Density} = \frac{W2 - W1}{W4 - W2}$$

8.8.5 Porosity:

Porosity is defined as the ratio of void volume to the bulk volume. It is calculated by using the formula:

$$\textbf{Porosity} = 1 - \frac{\textbf{Bulk Density}}{\textbf{True Density}}$$

8.8.6 Hausner Ratio:

It is the ratio of taped density to bulk density

Vo/ V_f

Where,

Vo = Bulk volume;

V_f = Tapped volume.

8.9 POST COMPRESSION EVALUATION OF THE TABLET:

The prepared tablets were subjected for various quality control tests in order to characterize them.

8.9.1 Weight Variation:

The weight variation test of the tablets was done as per the guidelines of Indian Pharmacopoeia. Ten tablets from each batch were weighed in digital balance and average weight was determined and standard deviation was calculated.

Weight Variation limits as per USP:

Average weight in mg.	% ± deviation allowed
130 or less	10
130-223	7.5
More than 324	5

8.9.2 Friability:

Friability is the measure of a tablet's ability to with stands both shock and abrasion without crumbling during the handling of manufacturing, packing, shipping and consumer use. The weight of 10 tablets was noted and placed them in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber, which revolves at 25 rpm, dropping the tablets a distance of 6 inches with the revolution. The pre-weighed tablet sample is removed after 100 revolutions, dusted and reweighed. Tablets that loose less than 0.5 to 1 percent in weight are generally considered acceptable.

$$\text{Friability (\%)} = \frac{\text{Initial wt. of 10 tablets - final wt. of 10 tablets}}{\text{Initial wt of 10 tablets}} * 100$$

8.9.3 Hardness:

Hardness of the tablet is an indication of its strength. It is tested by measuring the force required to break the tablet across the diameter. The force is measured in kg/cm2 and the hardness of about 4 kg/cm2 is considered to be satisfactory for uncoated tablets. Tablet requires a certain amount of mechanical strength to withstand the shock of handling during its manufacture, packaging, shipping and dispensing. It may be especially important to monitor the tablet hardness for sustained release drug products or other products that possess real or potential bioavailability problems are sensitive to variations in drug release profile. The crushing strength that just causes the tablet to break is recorded by means of Monsanto hardness tester.

8.9.4 Swelling index: [51]

The swelling and erosion studies were performed according to the method reported by Al-Taani and Tashtoush, to understand the influence of swelling and erosion behaviour on drug release. Matrix tablets were introduced into the dissolution apparatus under the standard set of condition as specified for drug release rate studies. The tablets were removed using small basket and the swollen weight of each tablet was determined. To determine the matrix erosion, swollen tablets were dried in a vacuum oven at 45^0C to a constant weight.

Calculations:

Swelling Index = (Mt-Mo)/Mo X 100

Where Mt – weight of tablet at time ‘t’

Mo – weight of tablet at time t=o

8.9.5 Drug content:

Accurately weigh 20 tablets and crushed in a motor; a quantity of powder equivalent to label claim Venlafaxine hydrochloride disperse in methanol, shake and dilute to 100ml with methanol and filter. Dilute 20ml of filtrate to 100ml with methanol. Measure the absorbance resulting solution at maximum at about 225nm by using UV-Visible spectroscopy.

Calculations:

$$\%\text{Drug content} = \frac{\text{Drug content}}{\text{Label claim}} * 100$$

8.10 DISSOLUTION TEST: [45]

Dissolution studies were performed using USP (II) standard dissolution apparatus at 37 ± 0.5ºC. The Tablet was placed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution Media used was distilled water.

During the test 10 ml of the sample was withdrawn at specific time intervals 30,60,90,120,150,180,240,360 and 480min after each withdrawal, same volume of fresh dissolution medium was added to maintain sink condition.

DISSOLUTION CONDITIONS:

Table no: 5 Dissolution parameters

S.No	Parameters	Specifications
1.	Apparatus	USP(II)
2.	Medium	water
3.	Volume	900ml
4.	Rpm	50
5.	Temperature	37±0.5°C
6.	Time interval	30,60,90,120,150,180,240,360 and 480min

8.11. Proposed mathematical models to explain the nature and mechanism of drug release from matrix tablets:[46,47,48]

8.11.1 Zero –order release model:

The zero order rate equation describes the systems, where the drug release rate independent of its concentration. The time verses % cumulative drug release graph was plotted.

$$Q_t = k_o t$$

8.11.2 First-order release model:

The first order rate equation describes the release from the systems,where release rate is concentration dependent. The time versus log of cumulative drug release graph was plotted.

$$I_n Q = I_n Q_o t$$

8.11.3 Higuchi square root model:

The equation describes the release of drug from insoluble matrix as square root of time dependent process based on Fickian diffusion .The square root of tme versus % cumulative drug release is plotted

$$Q_t = t^{1/2}$$

8.11.4 Korsmeyer- Peppas Model:

The model which represents a better fit for the formulations. According to this methods log of average percentage cumulative drug release versus log of time curve was plotted .From the slope value of exponent 'n' was calculated, and the value could be used to characterize different release mechanisms as

$$M_t / M_a = Kt^n$$

Table no: 6 Interpretations of Diffusion Mechanisms from Dosage Form

Release exponent (n)	**Drug transport mechanism**	**Rate as a function of time**
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super case-II transport	t^{n-1}

Where,

Q_t =Amount of drug release in time t'

Q_o =Initial amount of drug in tablet

S =Surface area oh tablet

K_O,K_1,K_H=Release rate constant of Zero order, First order, Higuchi rate equation.

M_t/M_a=fraction drug release in to dissolution medium

7.12 STABILITY STUDIES:[49]

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. . The purpose of stability testing is to provide evidence on

how the quality of a drug substance or drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted.

The different temperature and humidity condition, prescribed by the International Conference on Harmonization (ICH) for zone IV were employed namely [50]

1. 25^0C with 60% Relative humidity (RH)
2. 40^0C with 75% Relative humidity (RH)
3. Room temperature.

The ideal batches of the formulated matrix tablets containing 100 mg venlafaxine were packed in polyethylene bags and then kept in stability chamber at 25°C/60% RH, 40^0C/75% RH and room temperature. Samples were withdrawn at 15, 30 and 60 days and

evaluated for their physical appearance, drug content and in vitro drug release at specified intervals of time. T80 was also calculated by using dissolution studies. (Kulkarni G.T., 2004)

9. RESULTS AND DISSCUSION:

9.1 RESULTS:

9.1.1 PREFORMULATION STUDIES:

9.1.1 Development of calibration curve for Venlafaxine hydrochloride

Table no: 7 Standard curve for Venlafaxine hydrochloride.

Con of solution	Absorbance at 225 nm	Conμg/ml
5	0.203	0.203
10	0.370	0370
15	0.539	0.539
20	0.741	0.741
25	0.904	0.904

Standard curve graph for Venlafaxine hydrochloride

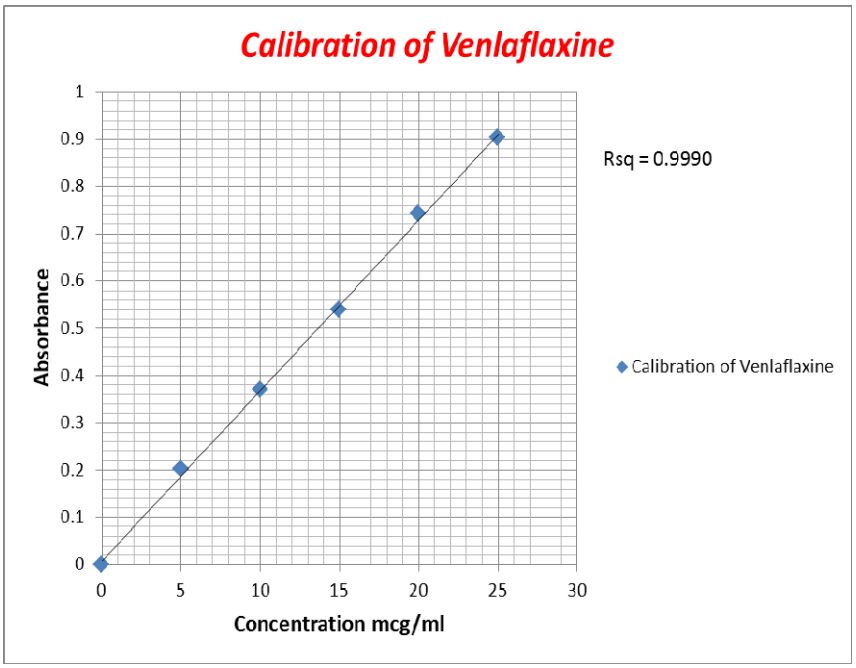


Figure no:5 calibration curve for Venlafaxine hydro chloride

9.2: Compatibility studies:

9.2.1: Table No: 8 Drug and Exicipient Compatibility study:

Sr. No	Name of the Excipient	API: Excipient	Initial Observation	Final observation		conclusion
				40°C/75% RH		
				2nd week	4th week	
1	API (venlaflaxin hydro chloride)	---	White crystalline powder	White crystalline powder	White crystalline powder	Compatible
2	API+ HPMC K15M	1 :1	White fine powder	White fine powder	White fine powder	Compatible
3	API + sodium alginate	1 : 1	White fine powder	White fine powder	White fine powder	Compatible
4	API + Avicel $P^{H}101$	1 : 1	White fine powder	White fine powder	White fine powder	Compatible
6	API + Mg. Stearate	1 : 0.05	White powder	White powder	White Powder	Compatible
7	API +Talc	1:0.05	White powder	White powder	White powder	Compatible

9.2.2: Sample no. 1: Venlafaxine hydrochloride

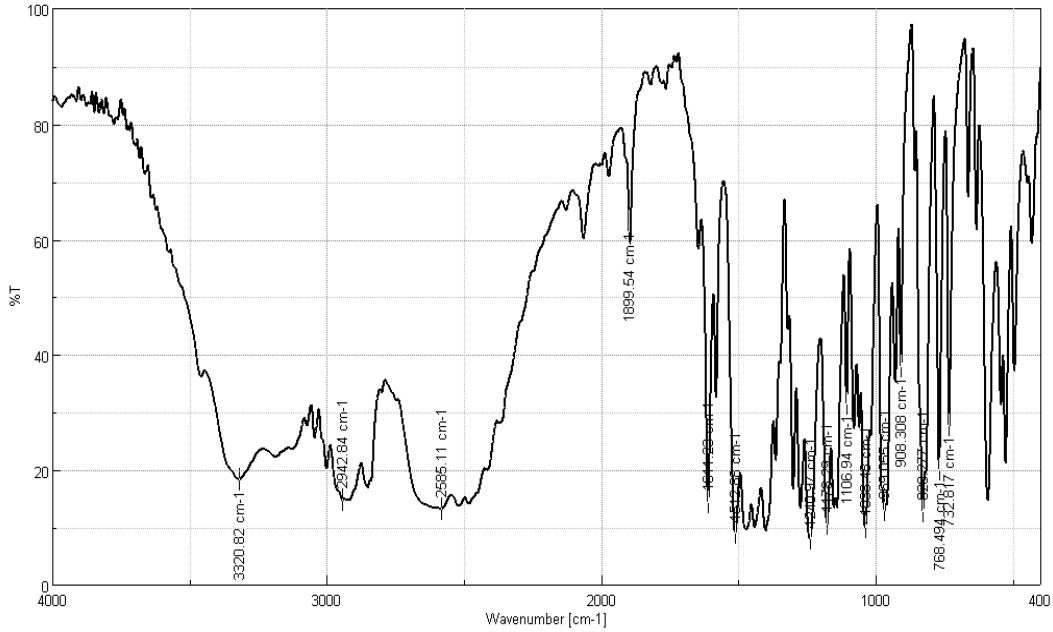


Figure no: 6 Venlafaxine hydrochloride.

9.2.3: Sample no.2: HPMC K15 M :

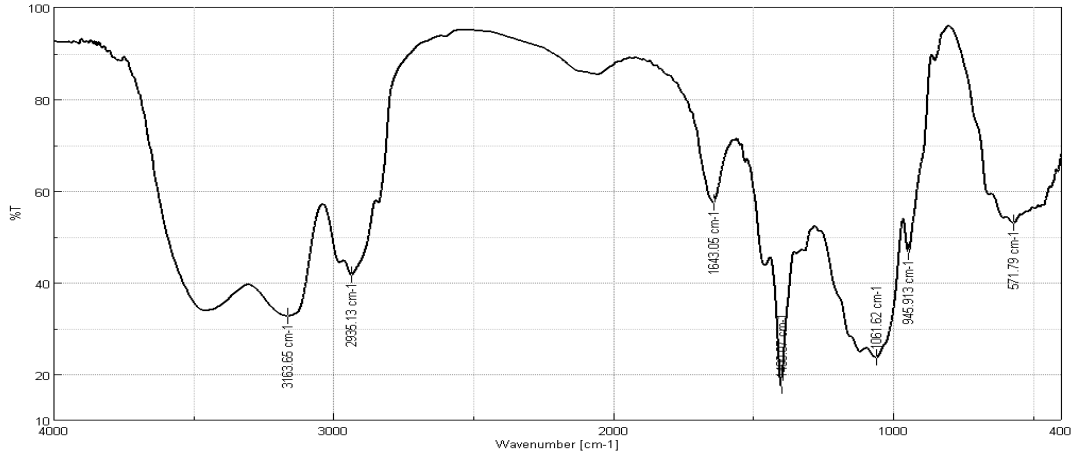


Figure no:7 HPMC K15 M

9.2.4: Sample no. 3: sodium alginate:

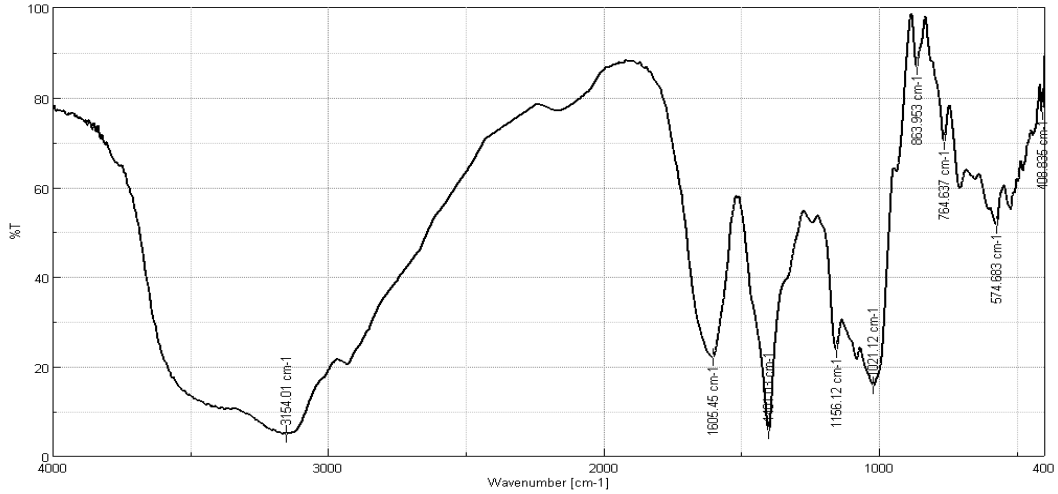


Figure no:8 Sodium alginate

9.2.5: Sample no. 4: Venlafaxine hydrochloride +HPMCK15M +sodium alginate

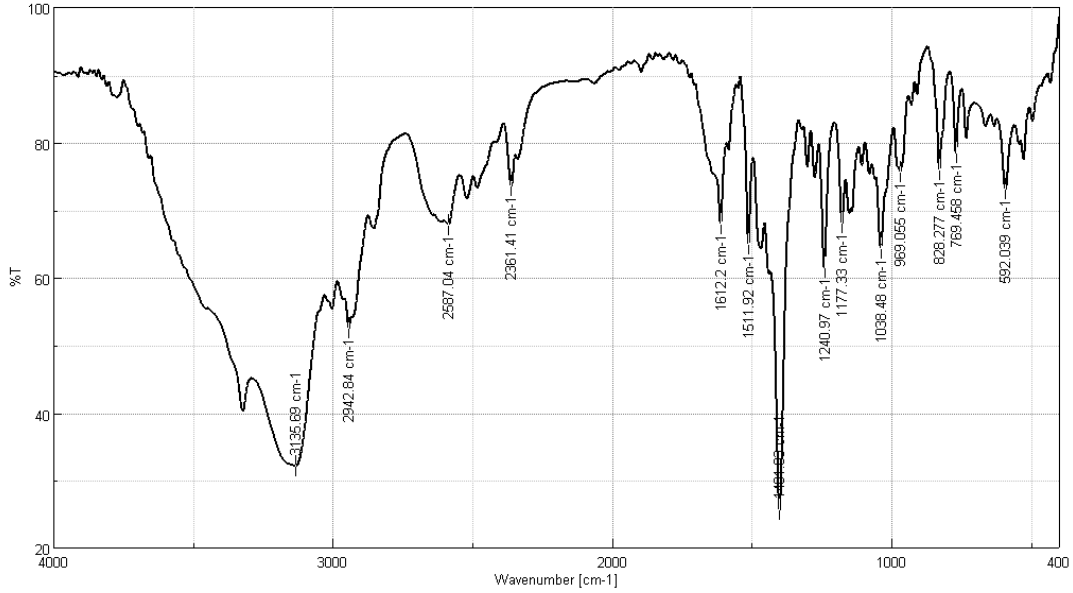


Figure no :9 Venlafaxine hydrochloride+HPMC+Sodium aliginate

TABLE NO:9 INTERPRETATION OF VENLAFAXINE HYDROCHLORIDE, HPMCK15M AND GRANULES CONTAINING WATER AS GRANULATING AGENT:

PEAKS Cm^{-1}	GROUPS	STRECHING/DEFORMATION
3320	O-H	Streching
1208	C-O	Streching
2875	Aliphatic C-H	Stretching
1245	Asymmetric C-O-C	Streching
1039	Symmetric C-O-C	Streching

9.3 PRECOMPRESSION RESULTS FOR EVALUATION OF VENLAFAXINE HYDROCHLORIDE GRANULES:

TABLE NO**:** 10

The prepared granules were subjected for various evaluation tests in order to characterize them.

FORMULAIONS	**F1**	**F2**	**F3**	**F4**
Angle of repose	19.73 ±0.453	18.24 ±0.234	17.23 ±0.211	17.92 ±0.116
Bulk density Tapped	0.463 ±0.012	0.481 ±0.010	0.474 ±0.013	0.488 ±0.025
Untapped	0.334 ±0.006	0.404 ±0.010	0.401 ±0.009	0.388 ±0.025
True density	16.969 ±1.031	16.20 ±0.905	14.26 ±0.923	21.0 ±1.218
Compressibility	0.638 ±0.047	0.617 ±0.032	0.621 ±0.029	0.631 ±0.010
% Porosity	27.087 ±1.731	21.989 ±1.062	13.928 ±1.801	22.55 ±1.711
Hausner ‘s ratio	1.204 ±0.015	1.190 ±0.014	1.195 ±0.022	1.259 ±0.015

FORMULAIONS	F5	F6	F7	F8	F9
Angle of repose	19.53 ±0.321	16.52 ±0.243	21.20 ±0.437	16.72 ±0.231	20.54 ±0.452
Bulk density Tapped	0.509 ±0.006	0.463 ±0.012	0.486 ±0.022	0.468 ±0.014	0.505 ±0.010
Untapped	0.378 ±0.010	0.334 ±0.006	0.398 ±0.011	0.402 ±0.004	0.362 ±0.052
True density	23.71 ±0.272	16.96 ±1.031	18.10 ±1.401	13.87 ±1.883	23.108 ±1.112
Compressibility	0.624 ±0.050	0.609 ±0.030	0.608 ±0.054	0.631 ±0.009	0.624 ±0.005
% Porosity	18.117 ±1.615	23.792 ±1.714	19.614 ±1.900	20.956 ±1.510	19.079 ±1.419
Hausner ‘s ratio	1.291 ±0.019	1.204 ±0.015	1.221 ±0.020	1.161 ±0.015	1.419 ±0.225

Table no: 9.3.1 evaluation of granules

9.4 POST COMPRESSION EVALUATION TESTS FOR PREPARED TABLETS:

Table no: 11 Evaluation of tablets for F1,F2,F3,F4,

FORMULATIONS	F1	F2	F3	F4
Weight variation	202.8 ±2.500	200.7 ±1.756	198.96 ±0.954	200.20 ±1.935
Friability	0.010 ±0.005	0.053 ±0.002	0.006 ±0.003	0.019 ±0.005
Hardness	4.700 ±0.208	4.100 ±0.100	4.333 ±0.152	3.700 ±0.200
Drug content	99.2 ±0.166	92.55 ±0.156	95.23 ±0.174	96.6 ±0.242
Swelling index	2.12 ±0.30	2.13 ±0.90	2.07 0±.043	2.04 ±0.223

Table no: 11 Evaluation of tablets for F5, F6, F7, F8,F9.

FORMULATIONS	F5	F6	F7	F8	F9
Weight variation	197.13 ±1.577	198.4 ±0.374	203.1 ±2.128	200.26 ±0.251	205.76 ±2.134
Friability	0.034 ±0.003	0.033 ±0.003	0.032 ±0.019	0.036 ±0.064	0.038 ±0.031
Hardness	4.0 ±0.200	4.100 ±0.100	4.500 ±0.351	4.233 ±0.251	5.00 ±0.100
Drug content	97.7 ±0.180	93.55 ±0.239	98.44 ±0.234	93.55 ±0.241	98.3 ±0.650
Swelling index	2.15 ±0.305	2.010 ±0.356	2.045 ±0.224	2.05 ±0.010	2.05 ±0.043

9.5 DISSOLUTION STUDIES:

TABLE NO: 12 DISSOLUTION STUDIES.

S.No	Parameters	Specifications
1.	Apparatus	USP(II)
2.	Medium	Distilled water
3.	Volume	900ml
4.	Rpm	50
5.	Temperature	37±0.5°C
6.	Time interval	30,60,90,120,150,180,240,360min

9.5.1 IN VITRO DISSOLUTION PROFILE OF FORMULATIONS:

Table no: 13 Release profile for formulations.

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	33.58	18.51	19.02	15.59	21.21	18.84	22.31	19.71	10.11
2	44.06	21.99	27.38	21.21	23.85	29.96	34.62	25.02	16.63
3	47.82	24.22	33.57	25.91	27.42	40.47	38.58	37.67	20.56
4	50.12	25.20	38.15	28.38	36.09	44.28	41.64	41.71	25.44
5	51.10	25.90	41.03	31.06	27.96	48.32	43.41	53.22	28.24
6	50.72	26.15	46.29	31.25	28.14	52.55	45.03	59.22	33.80
7	38.72	26.39	49.82	32.06	27.36	58.74	47.25	62.10	35.33
8	36.34	26.16	52.23	31.85	24.66	60.82	45.99	68.28	37.80
9	32.56	26.20	56.18	32.13	23.77	65.47	37.23	72.41	41.31
10	28.78	27.83	62.01	31.03	20.89	69.81	39.22	77.53	36.89
11	26.02	27.99	67.41	24.75	17.54	76.50	40.28	82.64	37.67
12	23.57	30.33	74.45	23.01	13.35	80.11	42.12	87.54	38.78
13	14.34	33.57	81.39	20.45	12.08	84.32	43.34	94.32	45.46

9.5.2 DRUG RELEASE PROFILE GRAPH FOR FORMULATINS F3,F6,F8:

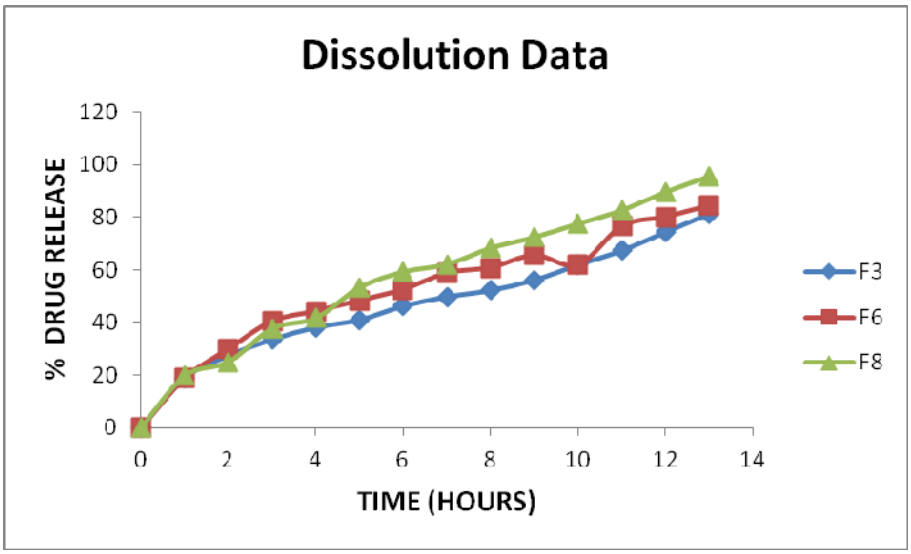


Figure no: 10 Invitro Drug release profile graph for Formulations F3, F6, F8.

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9 .5.3: t_{80}% DATA FOR FORMULATIONS F3, F6, F8:

Table no: 14 t80% data for formulations F3, F6, F8.

FORMULATION CODE	F3	F6	F8
TIME AT 80% OF DRUG RELEASED	12.80 hrs	11.70hrs	10.50hrs

9.6 KINETIC MODELS FOR DRUG RELEASED:

Table no: 15 kinetics model for F8:

TIME (Hrs)	Cu % DRUG RELEASE	% DRUG REMAINING	SQRT TIME	Log Cu % DRUG REMAINING	Log TIME	Log Cu % DRUG RELEASE
0	0.00	100	0.00	2.00	0.00	0.00
1	19.71	80.29	1.00	1.90	0.00	1.29
2	25.02	74.98	1.41	1.87	0.30	1.39
3	37.67	62.33	1.73	1.79	0.47	1.57
4	41.71	58.29	2.00	1.76	0.60	1.62
5	53.22	46.78	2.23	1.67	0.69	1.72
6	59.22	40.78	2.44	1.61	0.77	1.77
7	62.10	37.90	2.64	1.57	0.84	1.79
8	68.28	31.72	2.82	1.50	0.90	1.83
9	72.41	27.59	3.00	1.43	0.95	1.85
10	77.53	22.47	3.16	1.35	1.00	1.88
11	82.64	17.36	3.31	1.23	1.04	1.91
12	87.54	12.26	3.46	1.09	1.07	1.94
13	94.32	4.49	3.60	0.65	1.11	1.98

9.7 RELEASE MODELS GRAPH FOR OPTIMIZED FORMULA:

9.7.1 ZERO ORDER RELEASE MODELFOR F8:

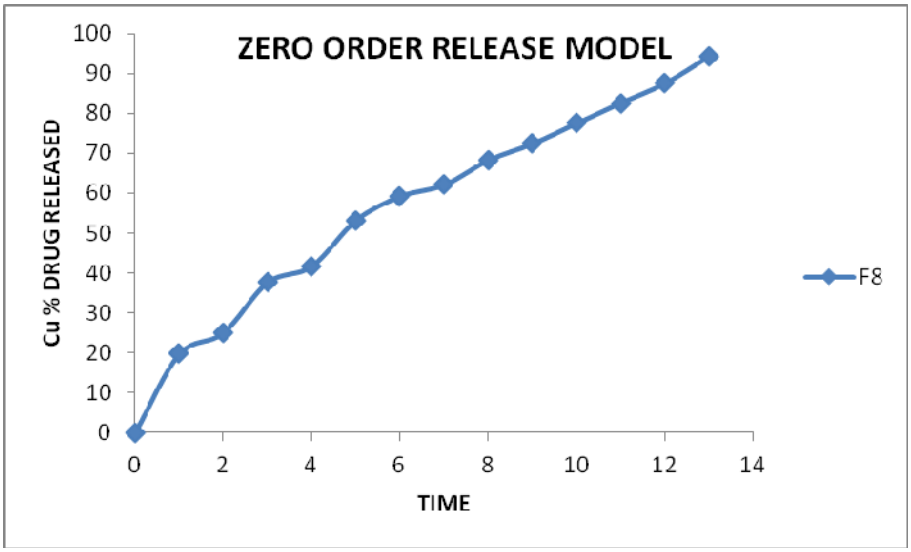

Figure no :11 Zero order release model graph for F8

9.7.2 FIRST ORDER RELEASE MODEL FOR F8:

Figure no : 12 First order release model graph for F8

9.7.3. HIGUCHI MATRIX MODEL FOR F8:

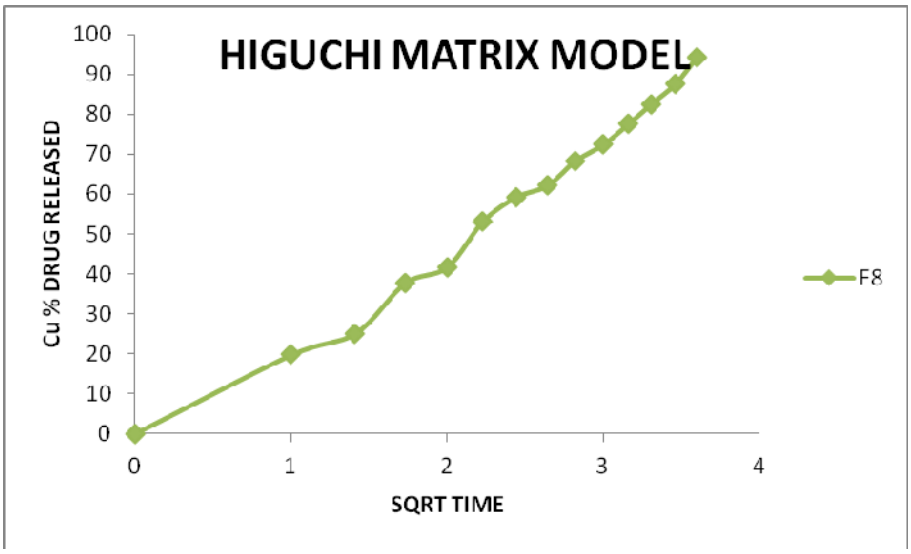

Figure no: 13 Higuchi model graph for F8.

9.7.4. KROSMEYER PEPPAS RELEASE MODEL FOR F3

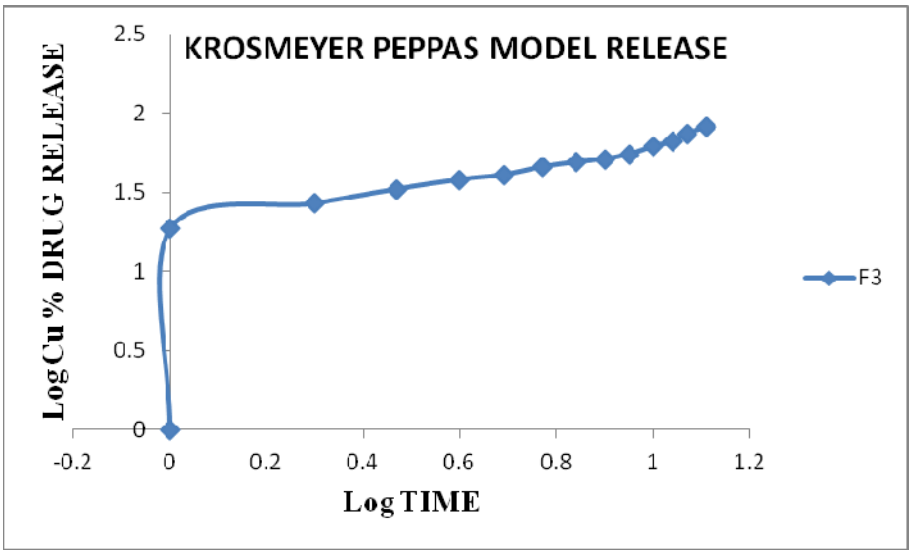

Figure no: 14 Krosmeyer order model graph for F8.

TABLE NO: 16 **R and N values from the above data**

FOMULATION CODE	**Zero order**	**1st order**	**Higuchi matrix**	**Peppas**	**N values**
F8 batch	_	0.6877	0.9245	0.9949	0.3017

Best fitting model is Peppas model

9.8 STABILITY STUDIES:

Table no:17 Stability study for F8.

s.no	**Evaluation parameters**	**F8 batch**		
		15 days	**30 days**	**60 days**
1	Physical Appearance	No significant change	No significant change	No significant change
2	Average weight (mg)	198.94 ±0.954	198.94 ±0.954	198.94 ±0.954
3	Hardness (kg/ cm^2)	4.332 ±0.152	4.332 ±0.152	4.332 ±0.152
4	Friability (%)	0.006 ±0.003	0.006 ±0.003	0.006 ±0.003
5	Swelling index	2.07 ±0.043	2.07 ±0.043	2.07 ±0.043

9.8.2 IN VITRO DISSOLUTION PROFILE OF VENLAFAXINE HYDROCHLORIDE MATRIX TABLET AFTER TWO MONTHS AT :

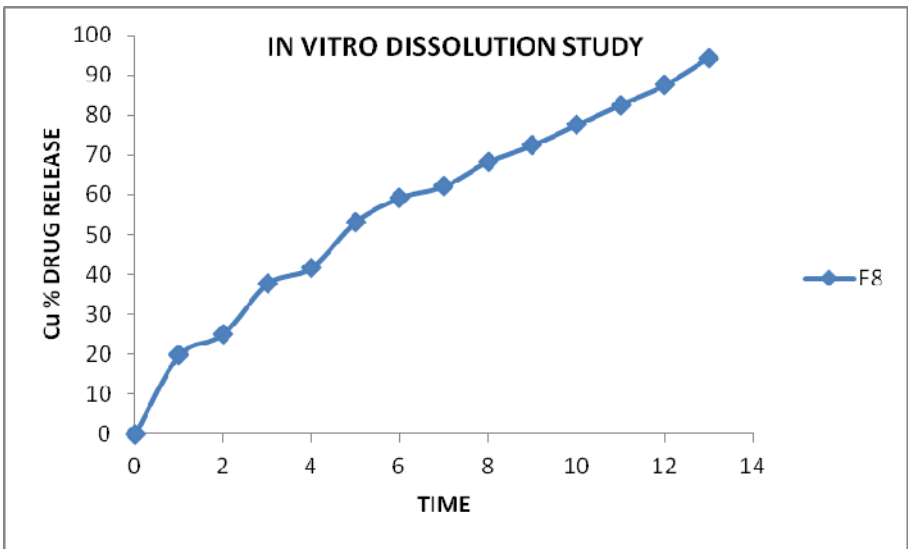

Figure no:15 Invitro dissolution study

9.9 DISSCUCUSION:

9.9.1 Development of calibration curve for Venlafaxine hydrochloride :

The scanning of drug solution in UV range showed maximum absorbance at 225 nm and hence, the calibration curve was developed at this wavelength. The calibration curve was linear between 5-25 μg/ml concentration range. The correlation coefficient 'r' was found to be 0.990.

9.9.2 Compatibility studies:

The compatibility between the drug and the selected excipients were evaluated using FTIR peak matching method. The IR spectra of pure drug, polymers and the physical mixtures are shown in figures. There was no appearance or disappearance of peaks in the polymer –drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymer.

9.9.3 Discussion for design and formulation of matrix tablet:

Venlafaxine hydrochloride sustained release matrix tablet was prepared by adding HPMC K15M as hydrophilic polymer, Sodium alginate as hydrophilic polymer, Avicel P^{H101} ,Magnesium stearate as lubricant and Talc as glidant.HPMCK15M is used retard the release drug from oral delivery system because of high viscosity. This extensive use originates from the non toxicity, high drug loading capacity and non P^{H} dependent of the polymer**.**

9.9.4 Evaluation of granules:

Venlafaxine hydrochloride granules were characterized for angle of repose, bulk density, true density, % porosity, Hausner ratio and Compressibility. The results were satisfactory. The granules were lightish white in colour, odourless, amorphous in nature and slightly bitter in taste.

9.9.5 Evaluation parameters for tablets:

Venlafaxine hydrochloride tablets were characterized for Weight variation, hardness, friability, and drug content. The results were satisfactory**.** The swelling index were statisfactory.The evaluated parameters were within acceptable range for all formulations. All the formulations pass the limit test.

9.9.6 Invitro drug release profile:

The formulated 9 batches were conducted dissolution for 13 hours and the sample was analysed and found the drug release. Satisfactory release was got in F3, F6 and F8 batches shows 81.39, 84.32 and 94.32.For the above data t_{80} % is calculated .These shows release at 10.50 hrs, 11.70 hrs and 12.80 hrs. As per t_{80}% F8 can be taken as optimized formula, this batch undergoes kinetic model. Best fitting model is Peppas model therefore considered as optimized formulations.

9.9.7 Stability studies:

Stability studies of F8 formulation Venlafaxine hydrochloride matrix tablet with HPMC K15 and sodium alginate were carried out at 25^{O}C/60% RH. There is no significant change in release characteristics and physicochemical properties of the tablets used in the release study. Based on the results it can be concluded that the formulated matrix tablets were stable at room temperature at different relative humidity over a period of 60 days.

F8 formulations were subjected to various evaluation parameters and the results obtained were within the range. The weight variation test indicates that all the tablets were uniform weight. Hardness of all the tablets were within the range of 4.23 Kg/cm^2.

9.9.8 Criteria for the selection of optimize formula:

Venlafaxine hydrochloride is an anti depressant drug. It belongs to the category Bio pharmaceutics classification (BCS) 1.This is a high solubility and high permeability drug. Venlafaxine hydrochloride sustained release matrix tablet was prepared by adding HPMC K15M as hydrophilic polymer, Sodium alginate as hydrophilic polymer, Avicel P^{H101} ,Magnesium stearate as lubricant and Talc as glidant.HPMCK15M is used retard the release drug from oral delivery system because of high viscosity. As per cumulative percentage of drug release satisfactory release was got in F3, F6 and F8 batches shows 81.39, 84.32 and 94.32.For the above data t_{80} % is calculated .These shows release at 10.50 hrs,11,70 hrs and 12.80 hrs .As per t_{80}% data F8 shows as a ideal formulation, this batch undergoes kinetic model. Best fitting model is Peppas model to this drug release .The N value of F8 is0.33, it follows Fickain diffusion.

10.SUMMARY AND CONCLUSION:

1. The aim was to develop a matrix formulation for oral delivery system for Venlafaxine hydrochloride using synthetic polymers to control release.

2. Based on the literature studies HPMC K15M and sodium alginate were choosen as a polymers for release rate control.

3.The selected polymer was characterized for swelling index which are essential for design of suitable matrix formulation In Preformulation studies, the compatibility between selected drug and polymer was tested by FTIR peak matching.

4.In the formulation development, a matrix, tablet of Venlafaxine hydrochloride were prepared using HPMC K15M and sodium alginate as a polymers and the effect of certain process and formulation variables such as compressional force, compressional time and concentration of polymer on the physicochemical and *in vitro* drug release was studied.

5.The kinetics of drug release was also determined by using Korsmeyer- Peppas equation.

6.In aging study, the ideal batches of the formulated matrix tablets were kept in stability chamber at 25°C/60% RH. Samples were withdrawn at 15, 30 and 60 days and evaluated for their physical appearance, friability, hardness, weight variation, swelling index and in vitro dissolution study.

All the above investigations brought out many facts, which lead to the following conclusions

10.The preformulation studies involving calibration curve development for the drug, and compatibility between selected drug and polymer was found to be better and incompatibility between drug and polymer shows that appears to be a better release rate control polymers for matrix formulation.

11.As per the time at which 80% drug released formulations F3,F6 and F8 was found to be 10.50,11.70 and 12.80 hrs.

12.The study on the various process formulation variables revealed that all the variables are important in developing a matrix tablet. A batch prepared with 40mg Hpmc K15M and 2.5 mg sodium alginate polymer concentration was identified as ideal batch based on its optimum hardness of 4.23kg/cm2 and percentage drug release was 94.32% F8 batch were found to be better.

13.The formulation F8 having ‘n’ value 0.33 less than 0.5.Then this formulation follows Fickain diffusion according to these F8 formulations are optimized formulation.

14.It is therefore expected to reduce cost and ultimately improve the patient compliance.

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